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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/158,272	09/22/98	DIAS	V 10806-64

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 01/19/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/158,272	Applicant(s) Dias Et. Al.
	Examiner Joseph Woitach	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 1 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *27-52* is/are pending in the application.

Of the above, claim(s) *29, 30, and 51* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *27, 28, 31-50, and 52* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *27-52* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The date of filing for the provisional application is incorrect, it was filed in 1997, not 1998.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a)-(d) and 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

There is no reference to the provisional for priority.

Claim Objections

Claim 28 is objected to because of the following informalities: Eukaryotes is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 31-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of using beta recombinase in mammalian cells which contain the HMG1 protein, it does not reasonably provide enablement for all eukaryotic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Specifically with respect to claims 27 and 43, the specification teaches that beta recombinase can catalyze site-specific recombination in mammalian cells. This is supported by Alonso *et al.* who teach that the Hbsu is required for the resolution and DNA inversion mediated by beta recombinase (JBC page 938; abstract), and that E.coli HU and/or mammalian HMG1 can substitute for Hbsu as a chromatin associated protein for *in vitro* mediated recombination (Molecular Microbiology page 471; abstract). Alonso *et al.* teach that this is a strict requirement,

and that in the absence of HU (in HU-deficient E. coli) or of another chromatin associated protein such as HMG1, recombination does not occur (JBC page 2943; figure 5). Neither the prior art nor the applicants demonstrate that beta recombinase is capable of mediating site-specific recombination in the absence of one of these proteins, therefore, any eukaryotic cell lacking expression of one of these proteins would be incapable of a recombination event (for example cells from the HMG1 knock-out mouse in Calogero *et al.*). It may be that other proteins will substitute for this requirement, however, this is not taught in the specification. Sequence homology does not seem to be a standard to judge whether other proteins can serve as a substitute since Hbsu and HMG1 do not share sequence homolgy but share a functional homology with respect to beta recombinase (page 2944; first line).

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 28 is drawn a method for controlling gene expression. The breadth of the claim is broad, encompassing the up- and/or down-regulation of a gene either permanently and/or transiently. The specification teaches a method by which using beta recombinase to generate a recombination event one could alter the expression of a gene by deletion of the DNA, however, the specification is silent with respect to specific target sequences and the consequential effect on of their modification on gene expression. The specification discloses no working example demonstrating changes in gene expression nor a description detailing a method to produce specific changes in gene expression. Further, the specification is completely silent with respect to modifying gene expression for transient and reversible changes in gene expression.

Further, even to one skilled in the art, the physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), and so the subtle control or transient change of gene expression encompassed in this claim is not described completely in the art.

Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The breadth of the claims is large, encompassing a method to produce a transgenic animal with any and all animals from the animal kingdom, including all mammals, reptiles, amphibians, birds, insects and other invertebrates. The specification does not teach the production of any transgenic animal, and while the specification does teach that one can use beta recombinase under certain cell culture conditions, there is no description nor working examples for use of embryonic stem cells which are known in the art to be capable of giving rise to a whole animal. At the time of the application, applicants admit that a transgenic mouse model is under development (page 13;

lines 27-30), and more recently, Diaz *et al.* also state that if confirmed in animal models (page 6639; last paragraph), indicating that the method to develop transgenic animals is still not enabled.

With respect to transgene expression, the physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The functionality of beta recombinase in different animal cells/tissues is untested and as discussed in the scope rejection *supra* with respect to requirement of HMG1, certain animals and eukaryotic cells may be resistant to development into transgenic animals because of the lack of beta recombinase activity in such cells. To successfully create DNA constructs capable of being used to create any animal, one would have isolate and characterize the gene sequences and promoters from each of the species that one would want to create. Further, the state of the art allows for the production of several transgenic animals, however, it is well recognized that transgene expression in different species can be variable, and so is unpredictable. This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth).

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 28, 31, 33-42, 48, 50, and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 27 is unclear in its recitation of "transgenic work". The claim and specification is drawn to a method of genetic manipulation using beta recombinase, however the method of this claim suggests a method to produce a transgenic animal which is taught in the specification.

Claim 27, 28 are method claims, however there are no method steps.

Claim 33 is vague unclear in its recitation of "two or more different specific recombination events at a time are promoted". The specification is clear in that the presence of beta recombinase and the appropriate factors result in a recombination event between two intramolecularly located *six* sites. It is unclear how "two or more different" events could occur in this context.

Claim 34 is unclear in its recitation of "exclusively". The specification teaches that in the context given in claim 32, only this intramolecular reaction will occur. To include exclusively in the claim implies that others may occur. If this is not the case, then claim 34 does not further limit claim 32.

Claims 35-39 are unclear in its recitation of "laying", and is also grammatically incorrect. Sustitution of 'inserted' is suggested.

Claims 39-40 are unclear in its recitation of "specific recognition sequences". The specification teaches that recombination occurs between *six* sites and no other recognition sequences have been described or defined.

Claim 48 is unclear in its recitation of "allocated". Sustitution of 'inserted' is suggested.

In claim 50 there is no antecedent basis in claim 43 for "the *six* sites".

In claim 52 the intended use for transgenic animal does not further limit claim 27. No additional steps are recited.

Conclusion

All claims are free from the art. There are two major families of site-specific recombinases; the Int and resolvase/invertase families. The prior art is replete with examples which use the Int family of recombinase for methods described in the specification (for example cre and flp), however, applicants were the first to isolate and describe the beta recombinase from the resolvase/invertase family. Further, applicants are the first to describe the method of use of beta recombinase in mammalian cells demonstrating that the mammalian HMG1 can serve as the required chromatin associated protein for resolution of site-specific recombination events.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax number for group 1600 is 1(703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Joseph T. Woitach

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800